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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,521	02/23/2002	Naoki Agata	1000.06.003	8046

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EXAMINER	
JONES, DWAYNE C	
ART UNIT	PAPER NUMBER
1614	5

DATE MAILED: 05/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/082,521	Applicant(s) AGATA ET AL.	
	Examiner Dwayne C Jones	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

1. Claims 1-20 are pending.

2. Claims 1-20 are rejected.

Information Disclosure Statement

3. The information disclosure statement filed on July 18, 2002 has been reviewed and considered, see enclosed copy of PTO FORM 1449.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of leukemia, colon tumors, reticulum blast sarcoma, breast cancer, lung carcinoma and myeloma, does not reasonably provide enablement for other types of cancer, such as cancer of the brain, prostate, ovaries, cervix, liver, pancreas, stomach, and skin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

6. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re

Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to inducing cell death in a cancer cell as well as inhibiting the proliferation of a cancer cell with the isocoumarin derivatives, glucocorticoids, and other chemotherapeutic agents.

(2) The state of the prior art

The compounds of the inventions are isocoumarin derivatives, glucocorticoids, and other chemotherapeutic agents. The prior art reference of Stein et al. teaches of the various causes of cancer, (see Chapters 71 and 72).

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art0; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the treatment of various types of cancers prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claims 1 and 7 are directed to treating a plethora of cancers via inducing cell death in a cancer cell and inhibiting the

proliferation of a cancer cell with the isocoumarin derivatives, glucocorticoids, and other chemotherapeutic agents of formulas. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of

the physiological or pharmaceutical activity of the instantly claimed compounds to be effective in treating prompt all types of cancer is insufficient for enablement. The specification provides no guidance, in the way of enablement for the treatment of other types of cancer other than those of leukemia, colon tumors, reticulum blast sarcoma, breast cancer, lung carcinoma and myeloma. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses the treatment various types of cancer by inducing cell death in a cancer cell as well as inhibiting the proliferation of a cancer cell with the isocoumarin derivatives, glucocorticoids, and other chemotherapeutic agents. However, the instant specification only has enablement for leukemia, colon tumors, reticulum blast sarcoma, breast cancer, lung carcinoma and myeloma.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the types of cancers that can be treated with the instantly claimed composition that would be enabled in this specification.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirano et al. of U.S. Patent No. 6,020,363. Hirano et al. teach of methods of treating diseases associated with an abnormality in immunological regulatory function or vascularization with derivatives of isocoumarin as defined by the compounds of formula (I), (see abstract and column 2, lines 30-49). Hirano et al. also teach that these isocoumarin compounds are useful in the treatment of malignant tumors and the like, (see column 7, lines 13-25 and lines 29-32). In addition, Hirano et al. teach that these compounds can be effectively and safely used without causing any appreciable toxicity, (see column 7, lines 38-42). The prior art reference of DiPiro et al. teaches of the chemotherapeutic coadministration of various chemotherapeutics, namely cyclophosphamide, vincristine and prednisone, (see page 1354). DiPiro et al. also

teach of the administration of inter alia, doxorubicin, cisplatin and BCNU, (see pages 1354 and 1355). Moreover, it would have been obvious to the skilled artisan to select other types of chemotherapeutic reagents, especially in view of the DiPiro et al. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, it would have been obvious to the one having ordinary skill in the art to combine these prior art teachings in order to arrive at the instantly claimed composition of isocoumarin derivatives with other chemotherapeutic agents, especially since all of these compounds are shown by the prior art to treat cancer.

10. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being obvious over Hirano et al. of U.S. Patent No. 6,020,363.

11. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR

1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2). Hirano et al. teach of methods of treating diseases associated with an abnormality in immunological regulatory function or vascularization with derivatives of isocoumarin as defined by the compounds of formula (I), (see abstract and column 2, lines 30-49). Hirano et al. also teach that these isocoumarin compounds are useful in the treatment of malignant tumors and the like, (see column 7, lines 13-25 and lines 29-32). In addition, Hirano et al. teach that these compounds can be effectively and safely used without causing any appreciable toxicity, (see column 7, lines 38-42). The prior art reference of DiPiro et al. teaches of the chemotherapeutic coadministration of various chemotherapeutics, namely cyclophosphamide, vincristine and prednisone, (see page 1354). DiPiro et al. also teach of the administration of inter alia, doxorubicin, cisplatin and BCNU, (see pages 1354 and 1355). Moreover, it would have been obvious to the skilled artisan to select other types of chemotherapeutic reagents, especially in view of the DiPiro et al. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the

very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, it would have been obvious to the one having ordinary skill in the art to combine these prior art teachings in order to arrive at the instantly claimed composition of isocoumarin derivatives with other chemotherapeutic agents, especially since all of these compounds are shown by the prior art to treat cancer.

Obviousness-type Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of Hirano et al. of U.S. Patent No. 6,020,363 in view of DiPiro et al. Hirano et al. teach of methods of treating diseases associated with an abnormality in immunological regulatory function or vascularization with derivatives of isocoumarin as defined by the compounds of formula

(I), (see abstract and column 2, lines 30-49). Hirano et al. also teach that these isocoumarin compounds are useful in the treatment of malignant tumors and the like, (see column 7, lines 13-25 and lines 29-32). In addition, Hirano et al. teach that these compounds can be effectively and safely used without causing any appreciable toxicity, (see column 7, lines 38-42). The prior art reference of DiPiro et al. teaches of the chemotherapeutic coadministration of various chemotherapeutics, namely cyclophosphamide, vincristine and prednisone, (see page 1354). DiPiro et al. also teach of the administration of inter alia, doxorubicin, cisplatin and BCNU, (see pages 1354 and 1355). Moreover, it would have been obvious to the skilled artisan to select other types of chemotherapeutic reagents, especially in view of the DiPiro et al. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, it would have been obvious to the one having ordinary skill in the art to combine these prior art teachings in order to arrive at the instantly claimed composition of isocoumarin derivatives with other chemotherapeutic agents, especially since all of these compounds are shown by the prior art to treat cancer.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (703) 308-

4634. The examiner can normally be reached on Mondays through Fridays from 8:30 am to 6:00 pm. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

DWAYNE C. JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
May 7, 2003